## Comments of R.J. Reynolds Tobacco Company ("RJRT")

### *Comment 1:*

The current California Environmental Protection Agency 2003 Draft Report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant," ("2003 Draft Report") does not support designation of environmental tobacco smoke ("ETS") as a toxic air contaminant ("TAC") in California. Additionally, the 2003 Draft Report reaches conclusions regarding ETS and breast cancer that are not supported by the record.[1] Furthermore, new data on ETS and breast cancer published since the 2003 Draft Report must be considered before a final Report is issued.

### *Response:*

*We address these general comments below in response to specific comments. Additional material, which has appeared in the literature since the appearance of the 2003 draft, has been reviewed and is described and evaluated in the latest version of the report.*

### *Comment 2:*

**The 2003 Draft Report Does Not Comply with the Statutory Requirements Pertaining to Designating a Substance as a TAC**

The California Environmental Protection Agency's ("Cal/EPA") authority to designate a substance as a TAC is not absolute. Specifically, Sections 39650-39674 of the California Health & Safety Code set forth several requirements that the Agency must meet before designating a substance as a TAC. For example, Section 39660 initially requires Cal/EPA generally to assess the exposure[2] and health effects[3] data for the substance and to specifically determine whether

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[1] Prior to the publication of the California Environmental Protection Agency's ("Cal/EPA" or "Agency") 1997 Report on ETS, RJRT submitted extensive comments to Cal/EPA explaining the basis for RJRT's disagreement with Cal/EPA's conclusions regarding ETS and health. Most of these comments were either rejected or ignored by Cal/EPA. Although RJRT stands by its previously submitted comments, those comments will not be revisited in this letter. Rather, this letter will focus on two issues that are specific to the 2003 Draft Report and thus not addressed in any previous comments by RJRT: 1) the failure of the current Draft Report to meet the requirements set forth in the California Statutes for designation of ETS as a TAC; and 2) the current Draft Report's causal conclusions regarding ETS and breast cancer.

[2] With respect to the ETS exposure assessment contained in the 2003 Draft Report, RJRT has retained Dr. Roger Jenkins to provide comments to Cal/EPA. Dr. Jenkins is a Group Leader and Distinguished R&D Staff Member at Oak Ridge National Laboratories. He has conducted and published extensive research regarding ETS chemistry and exposures. Dr. Jenkins' comments are based solely on his own expertise in this area and not on any input from RJRT.

current California ETS exposures are responsible for adverse health effects. If the Agency determines that current California ETS exposures are responsible for adverse health effects, then Section 39660 requires Cal/EPA to provide an estimate of the exposure level that may cause or contribute to adverse health effects in California, i.e., a California-specific risk assessment:

> (2) The evaluation shall also contain an estimate of the levels of exposure that may cause or contribute to adverse health effects. If it can be established that a threshold of adverse health effects exists, the estimate shall include both of the following factors:
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> (A) The exposure level below which no adverse health effects are anticipated.
>
> (B) An ample margin of safety that accounts for the variable effects that heterogeneous human populations exposed to the substance under evaluation may experience, the uncertainties associated with the applicability of the data to human beings, and the completeness and quality of the information available on potential human exposure to the substance. In cases in which there is no threshold of significant adverse health effects, the office shall determine the range of risk to humans resulting from current or anticipated exposure to the substance.

Cal. Health and Safety Code § 39660(2)

The 2003 Draft Report is completely devoid of any legitimate attempt to comply with these requirements. Assuming *arguendo* that the 2003 Draft Report has reached appropriate conclusions regarding ETS exposures and general health effects, the Report has not "estimated the levels of exposure [in California] that may be responsible for adverse health effects" in California. Moreover, the Report does not express any opinion regarding the existence or non-existence of a threshold level for ETS.

Rather than complying with the specific requirements set forth in § 39660(2), the Report employs an overly simplistic and wholly inappropriate approach to attempt to link ETS exposures with specific incidents of disease in California by utilizing the statistical concept of attributable risk[4] First and foremost, the use of attributable risk calculations requires the underlying epidemiology to be scientifically accurate. For the reasons set forth in RJRT's prior submissions to Cal/EPA, RJRT submits that the underlying epidemiology suffers from substantial scientific inaccuracies which only magnify the inappropriateness of using these studies for attributable risk calculations.

Second, the relative risks used in the attributable risk calculations are not applicable to the California population. The 2003 Draft Report contains no explanation of how the relied upon

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[3] With respect to the general health effects conclusions contained in the 2003 Draft Report, RJRT submitted extensive comments to Cal/EPA prior to the Agency's 1997 Report which explained the bases for RJRT's disagreement with these conclusions. Since the stated purpose of the 2003 Draft Report is to propose the listing of ETS as a TAC, RJRT will focus solely on the California-specific requirements set forth in Section 39660 which require the Agency to conduct a California-specific risk assessment for ETS.

[4] See Attributable Risk Table ES.2 on p. ES-11 and Table 1.2 on p.1-10.

epidemiology, even if scientifically accurate, has any relevance to the California-exposed population. The 2003 Draft Report takes great pride in distinguishing California ETS exposures as being substantially lower than the rest of the Country . [See ES-5, 6; IV-8, 9; Table IV-4] Thus, epidemiology studies conducted in other states (and even other countries) would necessarily be premised on populations with higher ETS exposures. Again, assuming *arguendo* that the relative risks from these studies are accurate, these studies provide only limited information about potential risks for the California-exposed population. Thus, using their relative risks for attributable risk calculations in California is wholly inappropriate.

Significantly, for at least three of the diseases that the 2003 Draft Report determined were causally associated with ETS, recent epidemiology studies based solely on California-exposed populations reported no causal association. In a prospective study of 118,094 Californians, Enstrom and Kabat concluded there was no causal association between ETS exposure and lung cancer or coronary heart disease[5]. James Enstrom subsequently petitioned the National Toxicology Program to delist ETS as a "known human carcinogen.."[6] Furthermore, in a 2004 study discussed in more detail later in these comments, Peggy Reynolds et al., prospectively followed 116,544 Californians and found no increased risk of breast cancer from ETS exposure[7].

Additionally, as correctly acknowledged in the 2003 Draft Report, these attributable risk calculations do not address whether there are risks from non-residential and non-workplace exposures in California. Since smoking is banned in practically all indoor environments in California other than in private homes and private automobiles, this omission renders the 2003 Draft Report useless for its stated purpose of determining whether current ETS exposures in California warrant designation of ETS as a TAC and future regulation of ETS in California.[8]

Finally, the flawed use of attributable risk calculations cannot be cured by developing better attributable risk calculations. The simplistic use of attributable risk calculations, regardless of the quality of those calculations, is not appropriate for meeting the requirements set forth in Section 39660(c)(2). While RJRT stands by its belief that ETS exposures in residential and occupational environments do not cause adverse health effects in adult nonsmokers, that is not the relevant

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[5] Enstrom, James E. and Kabat, Geoffrey C., Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960-98; BMJ, 326:1057-66 (2003). The study population was the California subset of the American Cancer Society cancer prevention study (CPS 1) that followed 1,078,894 adults from 25 states.

[6] See January 14, 2004, letter from James E. Enstrom to C.W. Jameson, Ph.D., of the National Toxicology Program. (Attached as "Exhibit A").

[7] Reynolds, Peggy, et a.1, Active Smoking, Household Passive Smoking, and Breast Cancer: Evidence from the California Teachers Study, J. Natl. Cancer Inst., 96(1): 29-37 (2004).

[8] Although the Exposure chapters of the 2003 Draft Report spend substantial verbiage attempting to estimate exposure to ETS from sources other than residential and occupational settings, the attributable risk calculations in the 2003 Draft Report make absolutely no effort to characterize any potential risks from ETS exposure in these environments. Therefore, the Report fails to meet this fundamental requirement set forth in the California statutes and does not satisfy the statutory definition of a TAC.

issue for purposes of determining whether the 2003 Draft Report complies with Section 39660(c)(2).

The relevant issue is whether current exposures in California warrant designation of ETS as a TAC and, if so, what are "the levels of exposure that may cause or contribute to adverse health effects [in California]." This issue cannot be evaluated by using attributable risk calculations. The epidemiology studies cited in the 2003 Draft Report do not analyze environments with exposures as low as those currently present in California. Even epidemiology studies that address past exposures in California may not be relevant for this purpose since the need for future regulation cannot be premised on exposure scenarios that no longer exist. Thus, the 2003 Draft Report does not comply with the statutory requirements set forth in Section 39660(c)(2).

## *Response:*

*OEHHA and ARB are advised by their respective legal counsels that the actions taken and proposed are appropriate. The intended purpose of the public comment period for the health effects document is to identify scientific issues in the report that may need further attention, rather than to debate any legal issues.*

*One issue, which OEHHA can address, is the comment that the attributable risk calculations are irrelevant for California. The comment fails to recognize that the lower smoking rates in California are factored into the calculations of attributable risk. There is no reason to believe that Californians would in fact not respond to ETS like other people, given the broad diversity of people present in California in terms of genetic, lifestyle, diet, and so forth.*

*Another issue is the implication in the comment that because Enstrom and Kabat did not find an association between ETS exposure and lung cancer or heart disease in the California population studied in ACS, that no such association exists for Californians. Enstrom and Kabat's paper is only one of many that have studied ETS exposure and lung cancer and/or heart disease. There is sufficient evidence from other investigations of a correlation between ETS exposure and both lung cancer and heart disease. As is often true in epidemiology, not every study of association between an exposure and disease is going to show a positive result even when the association is fairly strong given the vagaries of exposure ascertainment, particularly with ETS. The study by Enstrom & Kabat (2003) based exposure classification on spousal smoking at baseline in 1959. The study fails to control for other ETS exposures at a time when smoking, and hence ETS exposures were more pervasive. The study also fails to account for changing exposure of the "exposed" group over time, thus creating additional exposure misclassification. Indeed, in a*

*letter to the editor (http://bmj.bmjjournals.com/cgi/eletters/326/7398/1057#32482), Dr. Thun of the American Cancer Society noted:*

> ***"Scientifically, the fatal flaw of the paper is that the information collected on environmental tobacco smoke (ETS) exposure is insufficient to distinguish persons who were exposed from those who were not. When the study began in 1959, no information was collected on potential ETS exposure other on the smoking behavior of the spouse. At that time, exposure to second-hand smoke was pervasive in the United States and virtually everyone was exposed to ETS either at work, in social settings, or in other activities of daily living. Thus, the comparison group of "unexposed" persons whose spouses did not smoke was highly exposed to other sources of ETS, both before the study and during at least the first decade of follow-up. After 1972, the potential for misclassification of exposure was perpetuated and magnified, since no further information was collected on smoking by the spouse or on other sources of ETS exposure during the remaining 26 years of follow-up. Many of the spouses who reported smoking at the start of the study would have quit, died, or ended the marriage, yet the surviving partner was still classified as "exposed" in the analysis. The long duration of follow-up is a liability rather than a strength of the study with respect to the resultant misclassification of ETS exposure."***

## *Comment 3:*

**The 2003 Draft Report's Conclusions Regarding**
**Active Smoking, ETS and Breast Cancer Are Not Supported by the Record**

In 1997, Cal/EPA's Report on ETS examined four studies on ETS and breast cancer and determined there was insignificant evidence of a causal role[9]. Indeed, the 1997 Report did not even conclude that there was "suggestive evidence" of a causal association between ETS and breast cancer[10]. Now, six years later, after reviewing several new epidemiology studies with data remarkably similar to the four studies reviewed in the 1997 Report, the 2003 Draft Report concludes that ETS exposure is causally associated with breast cancer. This reversal of conclusions is not justified by the record[11].

## *Response:*

*The availability of new data and analyses since 1997 is one of the reasons why this update was undertaken. It is because of these new data, coupled with more rigorous analyses of the older data and use of information from the toxicology literature on carcinogens found in tobacco smoke, that the different conclusion on breast cancer was reached in the present report.*

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[9] 1997 Report, p. 7-44. Additionally, in 1997, the Cal/EPA Report referred to the alleged association between "active smoking" and breast cancer as "equivocal."

[10] 1997 Report, p. ES-2.

[11] At RJRT's request, Sanford Barsky, M.D. has submitted his own analysis of the 2003 Draft Report's breast cancer discussion and the literature on ETS and breast cancer. Dr. Barsky is a Professor of Pathology at the UCLA School

## *Comment 4:*

First, numerous public health agencies that have investigated the possible relationship between active smoking, ETS and breast cancer and reviewed the same data relied upon by Cal/EPA, have concluded that there is insufficient evidence of a causal role. Cal/EPA is the only one reaching a contrary conclusion[12].

The International Agency for Research on Cancer ("IARC"), the American Cancer Society ("ACS") and the National Cancer Institute ("NCI") all have evaluated the purported association between active smoking or ETS and breast cancer and concluded that the evidence is insufficient to link either smoking or ETS exposure with breast cancer. For example, in June 2002, IARC issued a press release on secondhand smoke carcinogenicity which stated "[c]oncern that breast cancer or any other cancer not caused by active smoking might be caused by involuntary smoking [ETS] is unjustified by the evidence."[13]t3 After an extensive literature review on the subject, IARC concluded that the prospective studies "provide no support for a causal relation" and added that the "lack of a positive dose-response argues against a causal interpretation."[14] The current ACS website on "What Causes Breast Cancer" does not list ETS among the "lifestyles" risk factors[15]. Furthermore, the ACS does not list active smoking as a risk factor and notes that a link between active smoking and breast cancer has not been found[16]. Likewise, the current NCI website on breast cancer risk factors ("Health Professional Version") does not include ETS or active smoking[17].

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of Medicine with special interest in breast cancer and lung cancer. Dr. Barsky's comments are based solely on his own expertise in this area and not on any input from RJRT.

[12] Admittedly, RJRT has not always agreed with the conclusions of various public health agencies regarding the association between ETS and disease. In many instances, RJRT's disagreement is premised on the difference between reaching causal conclusions that are based on valid scientific considerations versus those conclusions that are adopted by public health agencies and organizations which appear to be based on the "better safe than sorry" philosophy. While RJRT does not believe that many causal conclusions regarding ETS are supported by the science, we do recognize that public health agencies sometimes have a different standard for reaching causal conclusions to communicate to the public and the media. Therefore, when such agencies have reviewed the data on ETS and a disease such as breast cancer and have publicly stated that the evidence is insufficient to reach causal conclusions, this is particularly compelling and persuasive evidence that the scientific standard for determining causality has not been met.

[13] See httpJ/www.iarc.fr/pageroot/PRELEASES/nr141a.html (Attached as "Exhibit B").

[14] See http://www-cie.iarc.fr/htdocs/monographs/vol83/02-involuntary.html section 5.2. (Attached as "Exhibit C").

[15] http://www.cancer.org/docroot/CRI/content/CRI_2_4_2X_What_are_the_risk_factors_for_breast_cancer_5.asp?sitearea=. Revised 10/02/03. (Attached as "Exhibit D")

[16] Id.

[17] See http://www.cancer.gov/cancerinfo/pdq/prevention/breast/healthprofessional/ - Section 175, Revised 2/20/04. (Attached as "Exhibit E")

## *Response:*

*OEHHA values highly the assessments of IARC, NCI, and ACS. However, in undertaking evaluations of the scientific literature under our mandates for Toxic Air Contaminants, OEHHA makes an independent evaluation of the currently available data, and does not just follow without analysis the conclusions of other authorities. There are number of reasons why the conclusions of the Cal/EPA report may differ from other evaluations, such as that recently published by IARC. In the case of the association with breast cancer, we were able to include some studies and meta-analyses that were unavailable to IARC at the time of their report. OEHHA staff and consultants also undertook different (and more extensive) analyses of data than those used by IARC. In addition, the biological plausibility for an ETS link to breast cancer made in our analysis utilized information from the animal toxicology literature, which in our opinion has been given little consideration by these authorities (and epidemiologists in general).*

## *Comment 5:*

Second, well-respected epidemiologists in the public health community also have agreed that the evidence linking either smoking or ETS with breast cancer is insufficient to establish causality. For example, Jonathan Samet, M.D., senior scientific editor for the 2003 Surgeon General's report on active smoking and the Surgeon General's report on ETS that is currently being drafted[18], has stated that "investigation of cancer sites other than the lung should be guided by the data from active smokers and by appropriate toxicological evidence."[19] Without scientific consensus that active smoking has a causal association with breast cancer, scientists agree it is biologically implausible that ETS is causally associated with breast cancer.[20]

## *Response:*

*Some well-respected experts disagree with OEHHA's present conclusions, others agree with them, as is evident (inter alia) from the other comments received on this document. In addition, the premise that if there is insufficient evidence to link active smoking with a disease, then it is less likely that passive smoking would be a risk factor for that disease, is based upon the*

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[18] See the Johns Hopkins Bloomberg School of Public Health magazine, .http://www.jhsph.edu/Mag_Spring03/smokeout/expert.html. Additionally, on numerous occasions, Dr. Samet has served as an expert witness against the tobacco industry in smoking and health litigation.

[19] Samet, J.M. and Wang, S.S, Environmental Toxicants: Human Exposures and Their Health Effects, Chapter 10 - Environmental Tobacco Smoke, (2°d ed. 2000), 319-375, 349. (Attached as "Exhibit F")

*assumption that ETS is chemically identical to mainstream smoke. As noted elsewhere in these comments and responses, this is not correct, and concentrations of some carcinogens in ETS are much higher than in mainstream smoke (see response to comment 13 from LeVois). Additionally, it assumes a linear dose-response and similar toxicological interactions among ETS constituent as occurs among mainstream smoke constituents. In fact, there is evidence that the response is not linear, and that active smoking is anti-estrogenic which would mask carcinogenic effects on breast tissue, complicating the relationship between active smoking and breast cancer.*

## *Comment 6:*

Contrary to the opinions of every major public health organization and many well-respected epidemiologists who have reviewed the scientific literature on ETS and breast cancer, the 2003 Draft Report concludes that the evidence is consistent with a causal association between ETS and breast cancer. However, the Draft contains numerous errors, several misinterpretations and, in many cases, simply fails to explain how it analyzed key studies. First, the bases for the conclusion are wholly unclear, as the Draft does not specify on which data and studies it truly relies. Second, and more important, the data as a whole discussed or cited in the Draft (plus additional data Cal/EPA must consider) does not support a conclusion that a causal association exists between breast cancer and ETS. And finally, because the Draft's conclusion that active smoking causes breast cancer is flawed, it is biologically implausible to conclude that ETS causes breast cancer.

Providing Cal/EPA with meaningful comments on the 2003 Draft Report's section on ETS and breast cancer is difficult because Cal/EPA does not clearly explain on which studies and data it relies. The Draft discusses or cites to approximately 16 new studies on ETS and breast cancer published since the 1997 Report[21]. However, the Draft makes inconsistent references to the studies and inaccurate descriptions of the data. For example, Section 7.4.1.5 states that since its 1997 Report, "[f]our cohort and six case-control studies have reported on breast cancer risk and exposure to ETS."[22] The supporting parenthetical, however, cites a study on active smoking (Terry 2002)[23] and omits one of the cohort studies (Nishino 2001) that examines ETS and breast

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[20] Id.

[21] See Tables 7.4 E-M, pp. 7-122, 7-137: A precise determination of the number of studies considered in this section of the 2003 Draft Report is difficult since there is inconsistency between studies discussed and those listed in the various Tables. Note, for example, that the Marcus 2000 study is listed in Table 7.41 and two Morabia studies (1998, 2000) are listed in Table 7.4K, but they are not listed in Tables 7.4E or F. The Lui 2000 study is listed in Table 7.4E but not in 7.4F.

[22] Draft Report, p. 7-122.

[23] Terry, 2002. Interestingly, the Terry study observed a risk of breast cancer primarily in women who smoked 40 years or more. Little or no increased risk was observed in women who smoked less than 30 years. (pp. 724, 726). It

cancer risk[24]. Subsequently, in the section titled "Strength and Specificity," the 2003 Draft Report states "three new cohort studies ... reviewed for this update did not provide evidence of an association between ETS exposure and breast cancer risk....,,"[25] Once again, the Nishino cohort study is not included in the parenthetical. Does Cal/EPA rely on three cohort studies or four? Why is the Nishino study not cited with the other cohort studies? Why does the Nishino study receive only cursory discussion later in the section? These Nishino study omissions and the Draft's failure to explain the Nishino study's role in the analysis are especially troubling since Nishino is a statistically significant study showing a protective effect[26]. This type of inconsistency makes it impossible to determine what data Cal/EPA finds convincing enough to conclude a casual relationship exists between ETS and breast cancer.

## *Response*

*This comment appears to consist primarily of statements that the commentator found the document unclear or hard to understand, as well as general disagreement with our conclusion regarding an association between ETS and breast cancer. In reply, OEHHA notes the commentator's disagreement, but does not find any specific arguments here that would lead to modification of the report's conclusion. Some specific instances where extended explanations or improved descriptions are needed in the report have been identified as a result of these and other comments, and the draft report is being revised to address these. It is regrettable that the commentator found the report hard to follow, and we hope our revisions make the document clearer.*

*The document discusses Nishino, albeit briefly and does include it in Tables 7.4 E, 7.4F, and 7.4L. We did not ignore this study and do note in the text the presence of an inverse relationship*

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is biologically implausible that exposure to ETS increases the risk of breast cancer if direct smoking of 30 years or less does not.

[24] The Draft Report does briefly discuss the Nishino study later in the ETS section (p. 7-129), but why it fails to cite this study (twice) when listing cohort studies examining ETS and breast cancer risk is unclear. Thus, what weight, if any, Cal/EPA places on the Nishino cohort study in concluding that ETS causes breast cancer is uncertain. Interestingly, Cal/EPA's brief discussion of the Nishino study states, without further analysis, that the relative risk and confidence intervals are as follows: 0.58 relative risk, 95% confidence interval 0.34-0.99. Cal/EPA does not acknowledge that these results show a statistically significant protective effect of ETS on breast cancer. Furthermore, Table 7.4F incorrectly lists the Nishino as a statistically insignificant study with a confidence interval of 0.32-1.1. This type of inaccuracy is troubling and casts doubt on the reliability of Cal/EPA's analysis and conclusions.

[25] Jee 1999, Wartenberg 2000 and Egan 2002 in parenthetical.

[26] RJRT does not contend that the results of this study warrant a conclusion that ETS reduces breast cancer risk. Rather, this study - in combination with all other studies - further demonstrates that Cal/EPA's conclusions regarding ETS and breast cancer are not supported by the scientific literature.

*between ETS exposure and breast cancer risk in the study. Furthermore, the data are included in the summary statistics presented in the conclusion. This study unfortunately relied only on one question at baseline to ascertain exposure, and was likely to have missed significant other sources of exposure, as noted in Table 7.4F. The authors note in their discussion "In this study, women were not asked about their marital status in the baseline survey, so most unmarried women, who are a high-risk group for breast cancer, were categorized as not being passive smokers. This may have been why the breast cancer risk was lower with passive smoke exposure…". In regards to drawing conclusions based on these findings the authors state, "The relationship between passive smoking and breast cancer in this study should be interpreted with caution." Thank you for drawing attention to a typographic error in the text in regards to the confidence intervals. The confidence intervals for the study in the text should match those given in the tables 7.4F and 7.4L; 0.58 (CI 0.32-1.1). These are for the relative risk of breast cancer for non –smoking women whose husbands smoke adjusted for confounding variables (table 4 in Nishino et al, 2001). The significant data that are mentioned in your footnote are only adjusted for age and should not be used. In general, in this study adjusting for confounding did not make a difference in the results except for breast cancer; as you rightly point out, adjustment for age alone results in a statistically significant finding. However, adjustment for additional confounders moves the RR into a statistically non-significant category.*

*Given the difficulties in epidemiological studies, particularly with exposure ascertainment for ETS, it is not surprising that one of the many studies conducted would come up with an inverse relationship. The majority of studies show either null results or elevated risks.*

## *Comment 7:*

Furthermore, the "Summary of Risk Estimates" section discusses a review by Kenneth Johnson of 15 published studies and the summary risk estimates reached in this review. However, the Johnson review is "submitted" and is unavailable for independent analysis[27]. Thus, the methodology Johnson used in arriving at these risk estimates is unclear. Nor is it clear how much weight Cal/EPA places on Johnson's review. While the studies included in the Johnson review and the summary risk estimates are listed in Tables 7.4E-G (the first three tables in the Draft listing ETS studies), Tables 7.4H-M contain some studies not included in Tables 7.4E-G (and,

[27] 2003 Draft Report, p. 7-140. A PubMed search identified no Kenneth Johnson review on ETS or breast cancer published in 2003-04.

thus, apparently not included in Johnson's review). The importance placed on Johnson's review and on all other studies and data must be more clearly explained before RJRT or any member of the public can provide adequate and meaningful comment.[28]

## *Response:*

*In response to this comment and others, we have added more detail on the analysis, and have included more studies. This revised meta-analysis is presented in the revised report. Since this analysis is not primary research, and since all of the data utilized are presented in the original papers or in explanatory letters to the editor subsequent to publication, the analysis can be replicated by anyone using standard statistical techniques. The results of this exercise are used to give a quantitative assessment to the general qualitative impression generated by the contributions of mechanistic, toxicologic, and epidemiologic data supporting the role of ETS in causation of breast cancer.*

## *Comment 8:*

The difficulty in providing meaningful comment regarding Cal/EPA's analysis and methodology is compounded by the fact that the referenced studies provide no basis for Cal/EPA to change the conclusion reached in the Agency's 1997 Report, i.e., that there is insufficient evidence of a causal association between ETS exposure and breast cancer. For example, none of the studies reviewed in the 1997 Report show a relative risk point estimate equal to or below 1.0, but three of the studies since 1997 report relative risks equal to or below 1.0.[29] Of the remaining 13 new studies, more than half are not statistically significant[30]. 30 Thus, if anything, there is less scientific basis in 2003 to conclude that ETS is causally associated with breast cancer.

Cal/EPA tries to explain away the inconsistency between its 2003 breast cancer conclusion and the scientific data by arguing that some studies failed to include childhood or occupational ETS exposure with spousal exposure, resulting in artificially lower relative risk findings[31]. However,

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[28] Because of these concerns regarding the bases for Cal/EPA's conclusions in the 2003 Draft Report, RJRT requests an opportunity to comment again on the revised draft report if Cal/EPA does not change its conclusion that a causal association exists between ETS and breast cancer.

[29] Wartenberg, 2000, Nishino, 2001 and Lash, 2002. Furthermore, Wartenberg and Nishino are prospective studies. The Wartenberg study, funded by the U.S. Environmental Protection Agency among others, followed over 146,000 women prospectively and finds no association between ETS exposure and breast cancer death. The 2001 Nishino study followed 9,675 women prospectively and actually reports a statistically significant reduced risk of breast cancer among women exposed to ETS, as previously discussed.

[30] See Tables 7.4F and 7.41. Interestingly, the percentage of statistically significant vs. statistically insignificant studies is almost identical to the percentage in the 1997 Report, where half of the studies were statistically significant and half were not.

[31] See Report, pp. 7-128-30; 7-140; 7-147; Tables 7.4 F, 7.4 E.

Daniel Wartenberg replied to criticism that his study failed to include occupational exposure risks by stating his data showed no increased risk at work, at other locations, or all sources combined[32]. Moreover, the authors of the most recent study that includes childhood exposure in its analysis question the importance of childhood ETS exposure in breast cancer development[33] 33 Finally, IARC, ACS and NCI considered these same studies and do not differentiate between studies looking at only spousal exposure and those including childhood or occupational exposure. Cal/EPA appears to be making an arbitrary distinction for breast cancer that other scientific organizations looking at ETS and breast cancer risk fail to make.

Finally, the 2003 Draft Report's summary paragraph (p. 7-147) calls into question Cal/EPA's analysis of the data and bases for its conclusion by claiming that "in comparison to studies reviewed in the previous OEHHA report (Cal/EPA 1997), current epidemiological and toxicological data are substantially more indicative of a positive association between ETS exposure and breast cancer risk..." (emphasis added). This statement is false. In 1997, four studies were evaluated, all of which had relative risks over 1.0. Two of those four studies had relative risks over 2.0. The 2003 Draft Report evaluated several more studies. Looking at Table 7.4F from the Johnson review, three of the 11 new studies have relative risks of 1.0 or lower, and all three are recent, large prospective studies. Seven of the 11 studies are statistically insignificant. In reality, the 2003 Draft Report shows that the data considered in 1997 was more indicative of an association than the data presented in studies since 1997. The data in the Draft, considered as a whole, is substantially less indicative of a positive association between breast cancer and ETS exposure.

In addition to its ETS analysis, Cal/EPA also concludes in the 2003 Draft Report that a causal association exists between active smoking and breast cancer. The Draft only addresses direct smoking for biological plausibility, apparently in attempt to bolster an otherwise weak conclusion regarding ETS and breast cancer. Otherwise, this determination has no bearing on ETS as a TAC. RJRT disagrees with the Agency's conclusion that there is a causal association between active smoking and breast cancer.[34]

## *Response:*

*There are a number of new studies that do show significantly elevated risks particularly when exposure ascertainment was relatively better. In addition, the meta-analysis conducted with Johnson in our report (revised with additional studies added), demonstrates significantly elevated risks. Although many of the new studies did not necessarily indicate statistically*

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[32] Draft Report, p. 7-128, citing Wartenberg 2001.

[33] Kropp, p. 522. "Contrary to the assumption that breast tissue is more susceptible to carcinogens at young ages, early passive smoking may not play an important role in breast carcinogenesis."

[34] As discussed in the text above, a conclusion that active smoking is causally related to breast cancer is not consistent with the weight of the scientific evidence. Tables 7.4A&B list studies reviewed on direct smoking and breast cancer. The Tables demonstrate inconsistencies among the studies between the reported risks of breast cancer, and many studies lack statistically significant increased risks.

*significant elevations considered in isolation, most had point estimates above one and several indicated significant trend tests for elevated risk with a number of different metrics of exposure. Thus, we believe that taken together the older and newer studies, when analyzed thoroughly for better exposure ascertainment, and utilizing meta-analytic techniques provide evidence that ETS exposure is associated with breast cancer.*

*Due to the difficulties of ascertaining exposure to ETS in epidemiological studies, OEHHA sought to distinguish studies on the basis of how exposure was ascertained. The better the exposure (including questions not just about home, or work, or childhood, but about all environments, for example), the stronger the evidence for an association. This in itself provides evidence that there is an association. As noted here and elsewhere, although large prospective studies are often preferred over case-control studies, if the exposure assessment is poor, one does not necessarily gain a better understanding of causal associations relative to other study designs where the exposure assessment is better.*

## *Comment 9:*

**The 2003 Draft Report's Conclusions Regarding ETS and Breast Cancer Are Not Supported by More Recent Studies on ETS, Breast Cancer and Californians**

Additional data published since the release of the 2003 Draft Report further supports the conclusion that there is insufficient evidence that ETS is not causally associated with breast cancer. The Board must consider "all available scientific data" in determining whether a substance is a TAC[35]. On January 7, 2004, a new study was published examining breast cancer risk from active smoking and ETS exposure. See Reynolds, Peggy, et al., Active Smoking, Household Passive Smoking, and Breast Cancer: Evidence from the California Teachers Study, J. NatI. Cancer Inst.; 96(1): 29-37 (2004) ("Reynolds study"). (Attached as "Exhibit G"). Obviously, the Agency staff was unable to consider the Reynolds study in preparing the draft Report since the study was not published until after November 2003. Therefore, the 2004 Reynolds study is not included in the Report. Nonetheless, under California law, it must be considered before a final report is issued for consideration by the Board.

The Reynolds study is particularly pertinent to a Californian's risk of developing breast cancer from ETS. The Reynolds study population consists entirely of Californians - a large,

[35] See Cal Health & Safety Code §§ 39650, 39660. The California legislature determined that "the identification and regulation of toxic air contaminants should utilize the best available scientific evidence gathered from the public, private industry, the scientific community, and federal, state, and local agencies...." (§ 39650(d)). In evaluating the health effects associated with proposed TACs, "the office shall consider all available scientific data, including, but not limited to, relevant data provided by ... academic researchers...." (§ 39660(6)).

prospectively-followed cohort of female professional school employees from the California Teachers Study[36]. Studies have shown that breast cancer incidence varies from one geographic area to another[37]. No other study included in the 2003 Report involves a population of California cancer subjects. Thus, a study population consisting entirely of Californians has significant bearing on the risk Californians face of developing breast cancer from ETS exposure.

The Reynolds study "found no evidence of a relationship between household passive smoking exposure and breast cancer risk[38]. The hazard ratios for developing breast cancer from household ETS exposure were "close to unity for all passive smoking exposure categories examined." The hazard ratios ranged from .87 to 1.01 and were not statistically significant[39].

The Reynolds study is consistent with the four previous prospective studies that failed to find a statistically significant increased risk of breast cancer from ETS. Therefore, the five large prospective studies conducted since Cal/EPA's 1997 Report reach consistent results, and one study even reports a statistically significant protective effect from ETS. Moreover, these studies, which constitute a substantial portion of the data from the "new studies" reviewed by Cal/EPA since its 1997 Report, do not support an association between breast cancer and ETS exposure.

In summary, little has changed since 1997, when Cal/EPA correctly concluded that there was insufficient evidence linking ETS exposure and breast cancer. If anything, the additional data published since 1997 provide less support for a causal association between ETS and breast cancer than the pre-1997 data. Therefore, Cal/EPA's strained and novel assertion that a causal association exists between ETS and breast cancer is not supported by the scientific data.

## *Response:*

*OEHHA thanks this commentator (and several others) for drawing OEHHA's attention to this study, which appeared after preparation of the report's public review draft. OEHHA has included a summary and analysis of this study in the revised report, and also had discussions with the principal author as to the implications and conclusions drawn. It is important to note that the principal conclusion drawn by the authors of this study relates to active smoking, for which they found an association with breast cancer risk. It is incorrect to characterize the data*

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[36] "The CTS cohort was established from respondents to a 1995 mailing to all 329,000 active and retired female enrollees in the California State Teachers Retirement System (CaISTRS)." Reynolds, p. 30. 116,544 cohort members were followed from this mailing and 2,005 breast cancer subjects identified. Reynolds, p. 31.

[37] Reynolds, p. 29. Breast cancer is a disease of largely unknown etiology. See ACS website, NCI website, supra notes 13, 15; Millikan 1998, p. 377. Thus, it is not surprising persons in different geographic areas have different risks of developing breast cancer.

[38] Reynolds, p. 34.

[39] Reynolds, p. 31, Table 2.

*from this study as inconsistent with OEHHA's conclusion, since ascertainment of ETS exposure in the report so far published is limited.*

*We understand that prospective studies are favored study designs over case-control due to the lessened opportunity for bias. However, all the prospective cohort studies suffered from inadequate exposure characterization. Many relied on a single question regarding exposure to ETS at baseline and did not evaluate exposures in multiple environments (e.g., asked only about spousal smoking). Thus, although the prospective studies did not find statistical associations between breast cancer and ETS exposure, the study design limitations may at least partly explain the lack of association*

## *Comment 10:*

**Conclusion**

The 2003 Draft Report is insufficient to establish ETS as a Toxic Air Contaminant in California. Cal/EPA has not met the specific requirements for establishing a TAC laid out in Sections 39650-39675 of the California Health & Safety Code. Furthermore, the 2003 Draft Report's conclusion that a causal association exists between ETS and breast cancer is not supported by the current record and is inconsistent with additional scientific evidence not cited in the record.

## *Response:*

*OEHHA disagrees with the comment's conclusions; see responses to specific comments above.*